ACTIVE PHARMACEUTICAL INGREDIENTS COMMITTEE

A SECTOR GROUP OF CEFIC

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852
USA

Courtesy copy:
Dr. Roger Williams, Director
FDA/CDER
Office of Pharmaceutical Science
6027 Woodmont Office Complex 2
Rockville, MD 20852
USA

99 AUG 17 P2:11 03335

Docket No. 99N-0193

6 August 1999

Dear Sirs,

Please find hereunder the comments from:

CEFIC/APIC (European Chemical Industry Council/Active Pharmaceutical Ingredients Committee)
Avenue E. van Nieuwenhuyse 4, bte 2
B-1160, Brussels
Belgium
Contact person: Mr. Loïc Le Doré
Tel: +32 2 676 7212
Fax: +32 2 676 7301

on FDA's Proposed Rule on "Supplements and Other Changes to an Approved Application" (dated 18 June 1999).

CEFIC is the organization representing national federations, companies and more than 100 affiliated associations and sector groups, located in Europe. All together CEFIC represents directly or indirectly more than 40,000 large, medium and small chemical companies in Europe, which employ about 2 million people and account for more than 30% of the world's chemical production.
APIC is one of CEFIC's sector groups, comprising producers of active pharmaceutical ingredients (APIs) and intermediates in Europe. The major part of the total volume of APIs and intermediates imported into the USA originates from Europe. For this reason, CEFIC/APIC considers itself to be a very important stakeholder in new FDA Regulations and Guidances related to APIs and intermediates.

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We, therefore, highly appreciate this opportunity for submitting our European APIs- and intermediates manufacturing members' comments on the above mentioned Proposed Rule, which in part deals with changes relating to the manufacture of our products.

However, rather than submitting detailed comments on the Proposed Rule, CEFIC/APIC would like to refer to the comments it has submitted recently on the Draft Guidance documents underlying the Proposed Rule:

- Draft Guidance: "Changes to an Approved NDA or ANDA"
- Draft Guidance: "BACPAC I"

It is CEFIC/APIC's firm conviction that the, in many cases insurmountable, and merely procedural problems to get post-approval changes, relating to DMFs held by dedicated pharmaceutical bulk manufacturers, authorized, are the by far most important ones to be resolved first.
In view of the possibilities which CFR 314.70(a) offers for defining less burdensome change notification mechanisms within accompanying Guidance documents, we do not find it appropriate to specifically comment on the Proposed Rule.
Our proposal to FDA is to provide for realistic and workable filing mechanisms and requirements with regards to changes to DMFs within these underlying Guidance papers.
We, therefore, would like to refer to our above mentioned submitted comments on these Guidance papers, of which we enclose copies for your reference.

Sincerely yours,

Chris.Oldenhof, Ph.D.
Vice-President
CEFIC/APIC

Loic Le Doré,
APIC Secretary

- Enclosures (2)

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ACTIVE PHARMACEUTICAL INGREDIENTS COMMITTEE

A SECTOR GROUP OF CEFIC

Dockets Management Branch (HFA- 305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852
USA

Docket No. 98D-0994

Dear Sirs,

Please find hereunder the comments from:

CEFIC/APIC (European Chemical Industry Council/
Active Pharmaceutical Ingredients Committee)
Avenue E. van Nieuwenhuyse 4, bte 2
B- 1160, Brussels
Belgium
Contact Person: Mr. Loïc Le Doré
Telephone: + 32 2 676 7212
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on FDA's Draft "Guidance for Industry : BACPAC I" (November 1998).

CEFIC is the organisation representing national federations, companies and more than 100 chemical affiliated associations and sector groups, located in Europe. All together CEFIC represents directly or indirectly more than 40.000 large, medium and small chemical companies in Europe, which employ about 2 million people and account for more than 30% of the world's chemical production.
APIC is one of CEFIC's sector groups, comprising producers of active pharmaceutical ingredients (APIs) and intermediates in Europe. The major part of the total volume of APIs and intermediates imported into the USA originates from Europe. For this reason, CEFIC/APIC considers itself to be a very important stakeholder in new FDA Guidances related to APIs and intermediates. We therefore highly appreciate this opportunity for submitting our European APIs- and intermediates manufacturing members' comments on the Draft BACPAC I Guidance.

For already many years, CEFIC/APIC's greatest concern with regard to FDA's regulatory procedures has been the framework of requirements, procedures (and interpretations of these) in the area of bulk post-approval changes. In many situations it has appeared that the trajectories for obtaining FDA approval for the implementation of bulk post-approval changes are of such an extremely burdensome and complicated nature, that such approvals indeed appeared to be completely impossible to obtain! This has particularly been the case in situations in which an API or intermediate is being supplied by a manufacturer to a multitude of customers. In a significant number of these cases the (A)NDA- holders were even not the direct customers of the bulk product suppliers, which makes the post-approval changes approval process, as is has been till now, even more inappropriate and obstructive.

The seriousness of these problematic situations can be readily understood in view of the fact that many changes in the manufacture of pharmaceutical bulk products are absolutely necessary, or even mandatory for a great variety of reasons which may be of an environmental-, economical-, safety related-, quality improvement related- or other nature. It will, therefore, come as no surprise that CEFIC/APIC very much welcomes FDA's initiative to aim for implementation of bulk post-approval change procedures and requirements that will accommodate the implementation of improvements through changes within our industry's operations. We are convinced that both the FDA and industry agree that a basic starting point should be that it should be possible to effectuate changes for improvement, while safeguarding the safety and quality of drug products, and that change should not be hampered by the unnecessary complicatedness of the involved approval procedures. Since BACPAC I covers the area of intermediates, this guidance should especially focus on resolving the problems of suppliers of intermediates with special attention for those cases where intermediates are being supplied to the suppliers of APIs to (A)NDA holders.

CEFIC's overall view on the Draft BACPAC I Guidance:

It is beyond doubt that the Draft Guidance clearly illustrates FDA's sincere intention to develop a BACPAC that will be more accommodating to post-approval changes than has been the case up to this moment. The introduction of the data- and science-driven concept of "equivalence", to be determined as close to the point at which the change is implemented as possible, will be an enormously important achievement. Such concept will form a sound starting point for the science-based assessment of the actual impact of a change. Our below comments focus for a large part on the filing mechanisms and procedures proposed in the Draft Guidance for the various types of changes. More in particular, the basis for our comments is formed by practical implications and complications. Our principal starting point for these comments has been: "BACPAC procedures and requirements should resolve the crucial issue of any changes being made impossible for merely procedural reasons relating to filing mechanisms".

CEFIC/APIC's comments:

We have used the following system to indicated the relative importance of our comments:

***: Crucial. If the involved sections of the Draft Guidance will not be amended, BACPAC I will not be applicable/workable in practice and will therefore be of little value to both the FDA and industry.

**: Major. Amendments of the involved sections of the Draft Guidance will prevent serious problems in the area of bulk post-approval changes in the future.

*: Minor. These are recommendations aimed at improving the involved sections/aspects of the procedure in terms of clarity and/or applicability

Type * comment:**
Subject: Proven "equivalence" related to Supplements (CBES & PAS)
Relates to: lines 354-398 and 399-538 of the Draft.

As stated above, it is completely impossible in practice for suppliers of intermediates to obtain FDA-approval for any implementation of changes in situations that either

- involve a multitude of customers purchasing the intermediate, or
- imply that (A)NDA holders are not its direct customers (the more so if a multitude of direct customers and/or (A)NDA holders are involved),

if such a change will trigger the requirement for (A)NDA holders to submit supplements such as CBESs or even Prior Approval Supplements. In order to avoid that BACPAC I will make the implementation of changes in above situations completely impossible, even though equivalence at some intermediate point in the manufacture has been proven, CEFIC/APIC strongly appeals to the FDA to adjust the BACPAC I principles with regard to such CBES and PAS requirements. The most straightforward way to adjust the guidance in order to accommodate changes as described above, will be to allow for notification through Annual Updating (DMFs) plus Annual Reporting (ANDAs) instead of requiring Amendments (DMFs) plus CBESs or PASs (ANDAs), for all cases for which the latter requirements are listed in the Draft under the headings "Manufacturing Process Changes" and "Specification Changes".
It goes without saying that this comment does not intend to apply to changes for which "equivalence" has not been proven.

CEFIC/APIC would like to emphasize that installing an approval system for DMFs will be a highly attractive alternative to the above comment, which could be applied to the entire scope of BACPAC I and II. A similar system has been – very successfully!- in place for antibiotic APIs ("bulk AADAs"), but has regrettably been deleted as a consequence of the FDAMA. Applying "bulk AADA" approval principles to DMFs would, however, require certain modifications, such as:

- Limiting of review and approval to DMFs activated by reference by an (A)NDA holder. This to avoid workload increases at the FDA.
- Limiting of the approved status of a DMF to certain SUPAC categories, when relevant for drug product safety reasons.
- Including approval for DMFs on intermediates.

Because of the many straightforward advantages of a DMF-approval system, CEFIC/APIC would like to urge the FDA to take this possibility into very serious consideration. Apart from the practical advantages, it would allow FDA to assess certain changes before they will be implemented, as opposed to retrospective assessment through CBESs.

CEFIC/APIC has, furthermore, noted that in certain situations the FDA has accepted Final Intermediates to be designated as the Starting Material for drug applications. Such an approach will also bring relief to manufacturers of intermediates and will resolve the problem of the "unapprovable intermediates manufacturing changes", described above. CEFIC/APIC is aware that relatively higher requirements should be met in those cases concerning the inclusion of impurity limits in the to be submitted specifications of such Final Intermediates. CEFIC/APIC recommends to highlight this option within the BACPAC Guidance.

Type ** comment
2. Subject: Site changes related to CBE supplements

Relates to: lines 266 – 272 of the Draft

CEFIC/APIC recommends to downgrade the proposed CBES requirement for the listed site changes to an Annual Reporting requirement, provided that "equivalence" has been proven. CBES requirements for the described situations would lead to unnecessary regulatory burdens on suppliers and purchasers of intermediates and may again even render implementation of certain site changes impossible.

Type * comment:

3. Subject : Scope of the Guidance

Relates to: lines 1-8 of the Draft

CEFIC/APIC recommends, for the sake of clarity, to include in the Introduction the statement that the Guidance applies only to those changes which affect the contents of drug applications and/or DMFs.

4. Subject: Confidentiality of details of the change

Relates to: lines 75 – 77 of the Draft

CEFIC/APIC recommends to delete "at minimum" from this sentence, because it does not contribute anything to its meaning and may, on the other hand, create unclarity on this aspect.

5. Subject: Definitions of "site" and "facility"

Relates to: lines 217 – 231 of the Draft

For the sake of clarity, CEFIC/APIC recommends to include the definitions of the words "site" and "facility" in the Guideline's "Glossary of Terms".

6. Subject: Clarification

Relates to: lines 232 – 272 of the Draft

CEFIC/APIC recommends, for clarification purposes, to insert a statement that this section only applies to site changes which are not within a single facility.

7. Subject: Scale changes

Relates to: lines 274 – 278 of the Draft

CEFIC/APIC recommends to add here that the section only applies to scale changes outside the ranges included in the application or DMF.

8. Subject: Analytical validation

Relates to: lines 333 – 334 of the Draft

CEFIC/APIC recommends to insert between the words "new" and "analytical": ", non-compendial," for the sake of clarity.

9. Subject: Tightening of acceptance criteria

Relates to: line 340 of the Draft

Tightening of acceptance criteria may be the result of specific demands of some of the customers who purchase the bulk product, or of considerations of competitiveness of product quality. Therefore this is not necessarily related to drug product safety. CEFIC/APIC recommends to clarify here that submission of information on tightening of acceptance criteria is not mandatory per se.

10. Subject: Change-control protocol
Relates to: lines 503 – 505 of the Draft

CEFIC/APIC would like to emphasize that, according to established FDA policies, change-control protocols are documents which should be available in-house for internal use, available for review and assessment by FDA inspectors. Such documents should, therefore, not be included in submissions. We recommend to delete these lines from the Draft.

11. Subject: Synthetic peptides
Relates to: lines 17 – 20 of the Draft

We have a question on this section:
Why are synthetic peptides excluded from the scope of the Draft? Are there plans for another document that will deal with post-approval changes for syntethic peptides or how will these changes be dealt with by the agency?

CEFIC/APIC would like to express its strong commitment to supporting the FDA in developing a successful, but also applicable in practice, BACPAC Guidance. We, therefore, trust that our above comments will be taken very seriously into account in preparing the final draft guidance.
Our organisation is fully prepared and willing to provide further BACPAC input whenever required, with the aim of avoiding a future in which any beneficial changes related to bulk pharmaceutical manufacture will be obstructed by prohibitive procedural issues only.

Sincerely yours,

L. Le Doré
Secretary General to CEFIC/APIC

ACTIVE PHARMACEUTICAL INGREDIENTS COMMITTEE

A SECTOR GROUP OF CEFIC

8-16-99

Dockets Management Branch (HFA-305)
Food and Drug Administration
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USA

Courtesy copy:
Dr. Roger Williams, Director
FDA/CDER
Office of Pharmaceutical Science
6027 Woodmont Office Complex 2
Rockville, MD 20852
USA

Docket No. 99D-0529

6 August 1999

Dear Sirs,

Please find hereunder the comments from:

CEFIC/APIC (European Chemical Industry
Council/Active Pharmaceutical Ingredients Committee)
Avenue E. van Nieuwenhuyse 4, bte 2
B-1160, Brussels
Belgium
Contact person: Mr. Loïc Le Doré
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on FDA's Draft "Guidance for Industry: Changes to an Approved NDA or ANDA" (June 1999).

CEFIC is the organization representing national federations, companies and more than 100 affiliated associations and sector groups, located in Europe. All together CEFIC represents directly or indirectly more than 40,000 large, medium and small chemical companies in Europe, which employ about 2 million people and account for more than 30% of the world's chemical production.
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Europe. For this reason, CEFIC/APIC considers itself to be a very important stakeholder in new FDA Guidances related to APIs and intermediates.
We, therefore, highly appreciate this opportunity for submitting our European APIs- and intermediates manufacturing members' comments on the above mentioned Draft Guidance, which in part deals with changes relating to the manufacture of our products.

The API related aspects of the Draft Guidance on "Changes to an Approved NDA or ANDA" are closely linked to those which were included in FDA's recently issued Draft "BACPAC I" Guidance (as well as to the yet to be issued Draft "BACPAC II" Guidance). Therefore, the majority of CEFIC/APIC comments on the Draft "BACPAC I" Guidance, which we recently submitted to the FDA, are of direct relevance to this newly issued Draft Guidance as well.
For this reason, we enclose a copy of our previously submitted comments on the "BACPAC I" Draft Guidance for your reference, instead of repeating them here.

We find it important to emphasize that our previously submitted comments on the BACPAC I Draft, which were designated as Type *** and Type ** comments, were not intended to plead for somewhat more flexibility within the proposed procedures and requirements for getting post-approval changes authorized. These comments actually originated from the much more serious concern that the proposed procedures and requirements would result in the impossibility for dedicated API- and intermediates manufacturers, who are holders of DMFs, to get (often unavoidable) post-approval changes authorized at all.
We refer to page 3 of the enclosure for an explanation on the reasons for this, obviously highly undesirable, result of the proposed BACPAC I Guidance. Suggestions from CEFIC/APIC for resolving this problem are also described on that same page.

Since the Draft Guidance "Changes to an Approved NDA or ANDA" includes proposals for API-related post-approval changes procedures and requirements which are very similar to those which were included in the BACPAC I Draft, we would like to request FDA to take our comments and suggestions once more into serious consideration, now with regards to this new Draft Guidance.
The contents of the new Draft Guidance indicates that the comments received by FDA from industry on the BACPAC I Draft have not yet been taken into account during its drafting.

Since the new Draft Guidance also covers the scope of the yet to be issued BACPAC II Draft, we would like to refer again to the suggestions we have included on page 3 of our previously submitted comments. These suggestions cover the entire scope of BACPAC I plus II. They are intended to resolve the entire problem of post-approval change authorization obstructions for DMF holders, whether involved in API- or in intermediate manufacture.

Because CEFIC/APIC regards the above mentioned procedural problems for DMF holders of a paramount importance, which supersedes all other possible needs to fine-tune the Draft, we have decided to refrain from submitting any additional, more detailed comments on the contents of the Draft Guidance.

As stated in our previous comments, CEFIC/APIC does not believe that it is FDA's intention to fully obstruct the implementation of beneficial post-approval changes to bulk pharmaceutical manufacture, because of inadequacies within the available filing mechanism procedures only.

CEFIC acknowledges the need for stringent change control regulations to ensure all appropriate measures are taken to safeguard public health. Nevertheless, the current regulations only apply to changes to approved NDAs and ANDAs, which entails that companies importing into the US and selling only to OTC producers are unaffected by these regulations. Over a thousand tons of APIs for the OTC market are imported every year into the US, often without verification of cGMP compliance and where unannounced process changes or changes relating to the origin of supplies are possible.

These companies are subjected to the cGMP change control regulations, however, without verification as no pre-approval and hence, no-follow-up audits are generally involved.

A dramatic example (37 deaths and 1500 permanent disabilities) that readily available molecules can become life-threatening is L-tryptophane, a nutritional supplement banned by the FDA in November 1990. Initially genetic engineering was blamed, but later, changes in the purification techniques appeared to be the causative factor.

This is a clear example where differences in regulations between OTC and prescription drugs is unjustified. No such difference exists in the European Union where the variations regulations apply to all drugs substances, regardless of their prescription status.

CEFIC/APIC would once more like to express its strong commitment to support the FDA in the development of realistic and workable post-approval change Guidance in the area of pharmaceutical bulk manufacture.

Our organization is fully prepared and willing to provide further input and clarification, whenever required.

Sincerely yours,

Chris Oldenhof, Ph.D.
Vice-President
CEFIC/APIC

Loic Le Doré,
APIC Secretary

- Enclosure